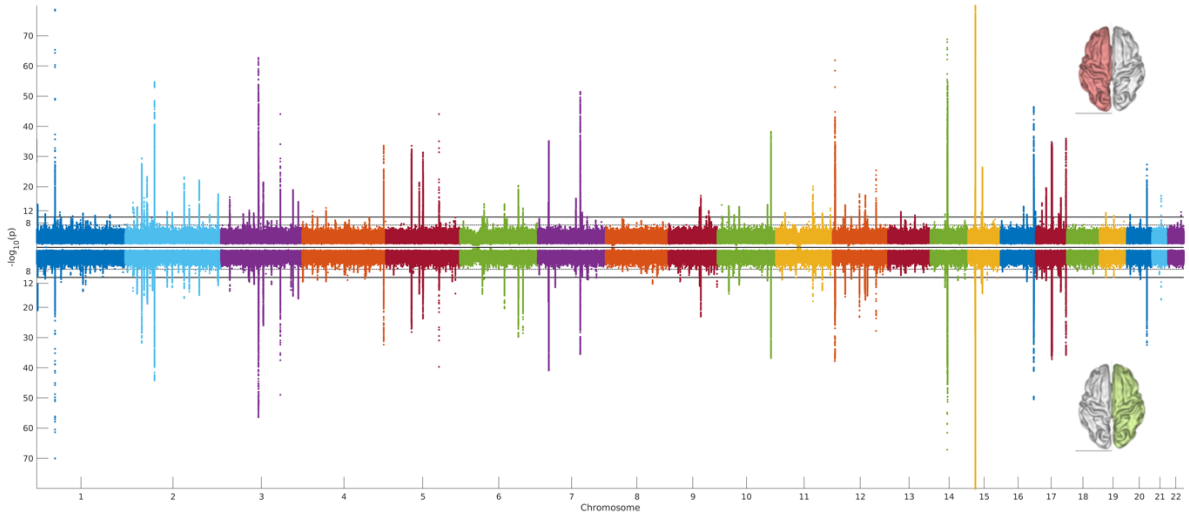
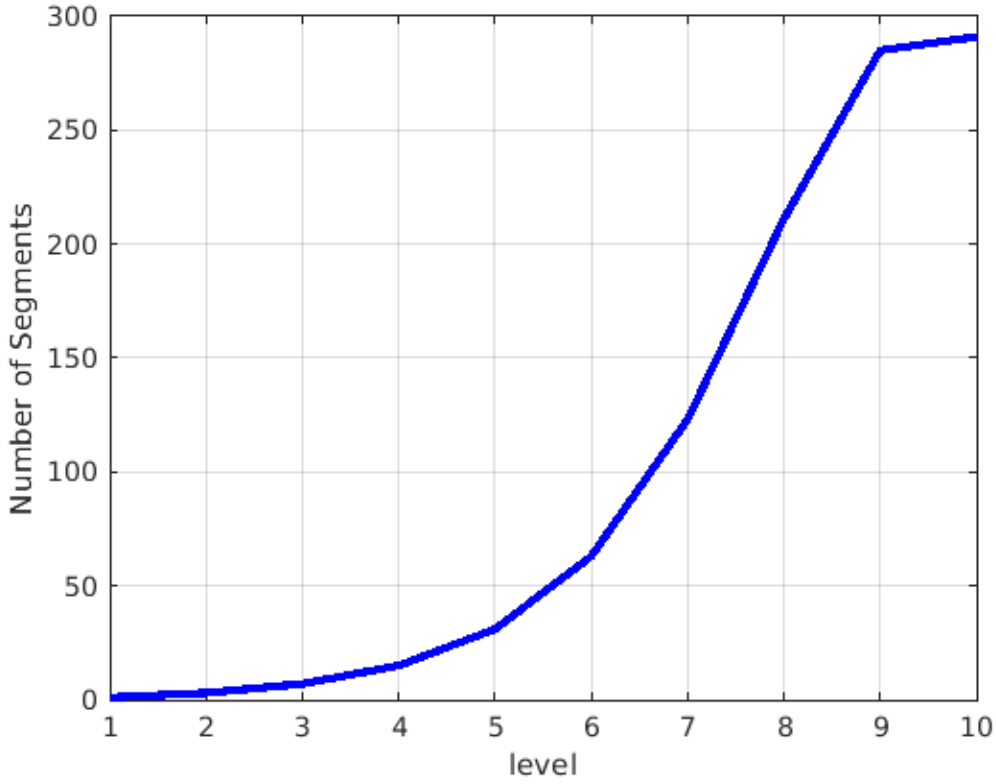
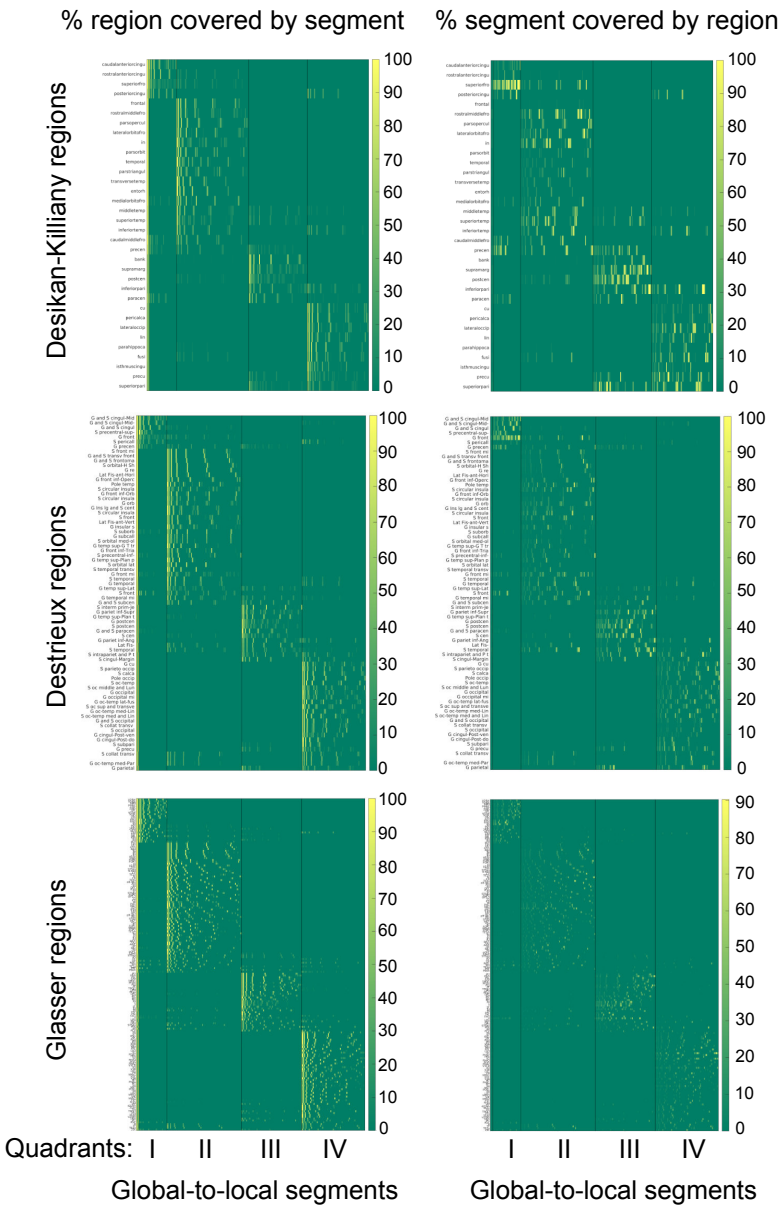


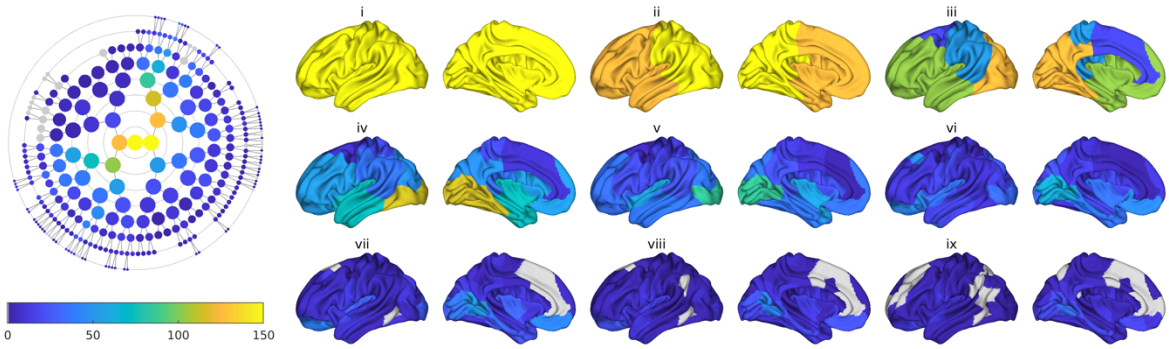
Supplementary Fig. 1 Miami plot of brain shape in left (top) and right (bottom) hemispheres in the UK Biobank. Global-to-local segmentation and CCA-based GWAS was performed independently within each hemisphere, but using data from the same individuals in UKBB. For each SNP, the aggregated p-values across all left (n=241) or right (n=201) hemisphere segments are plotted.



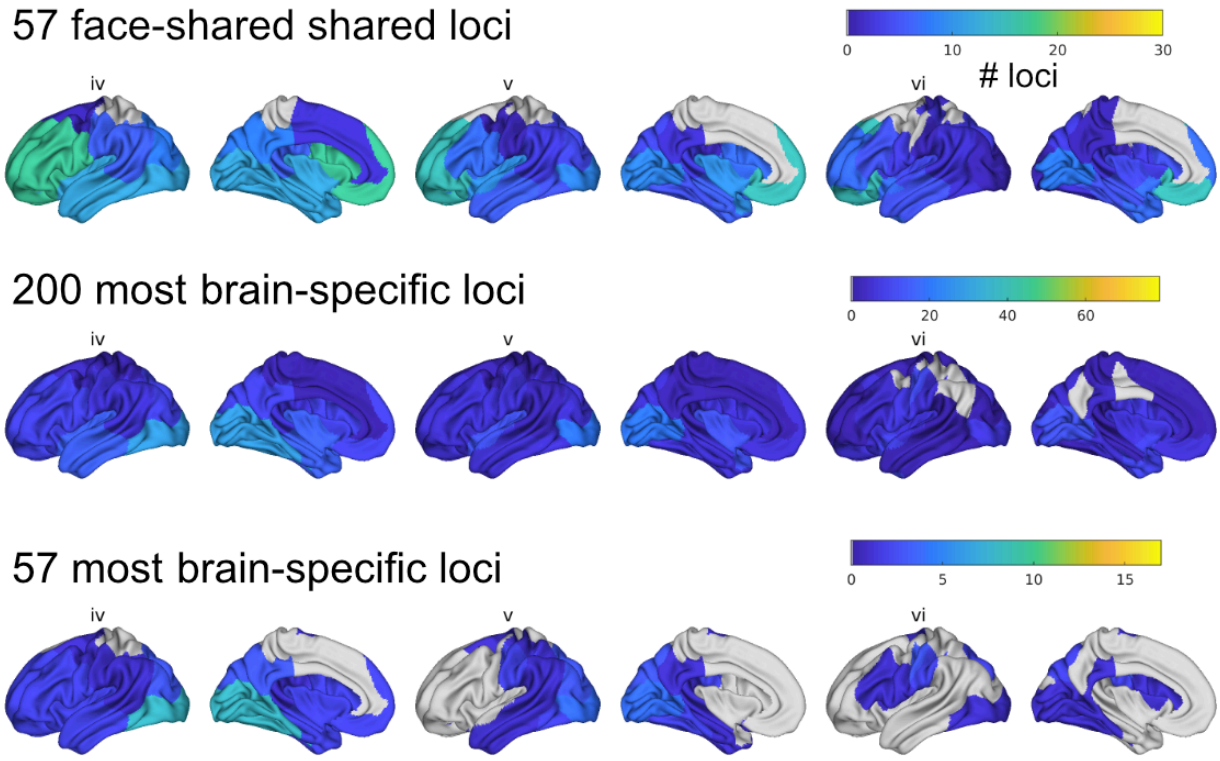
Supplementary Fig. 2 Total number of segments obtained after global-to-local segmentation with the indicated number of hierarchical levels. Note the large numbers of additional segments passing the 1% vertex cutoff contributed up to the ninth hierarchical level (the maximum used in this study), after which relatively few new segments are contributed.



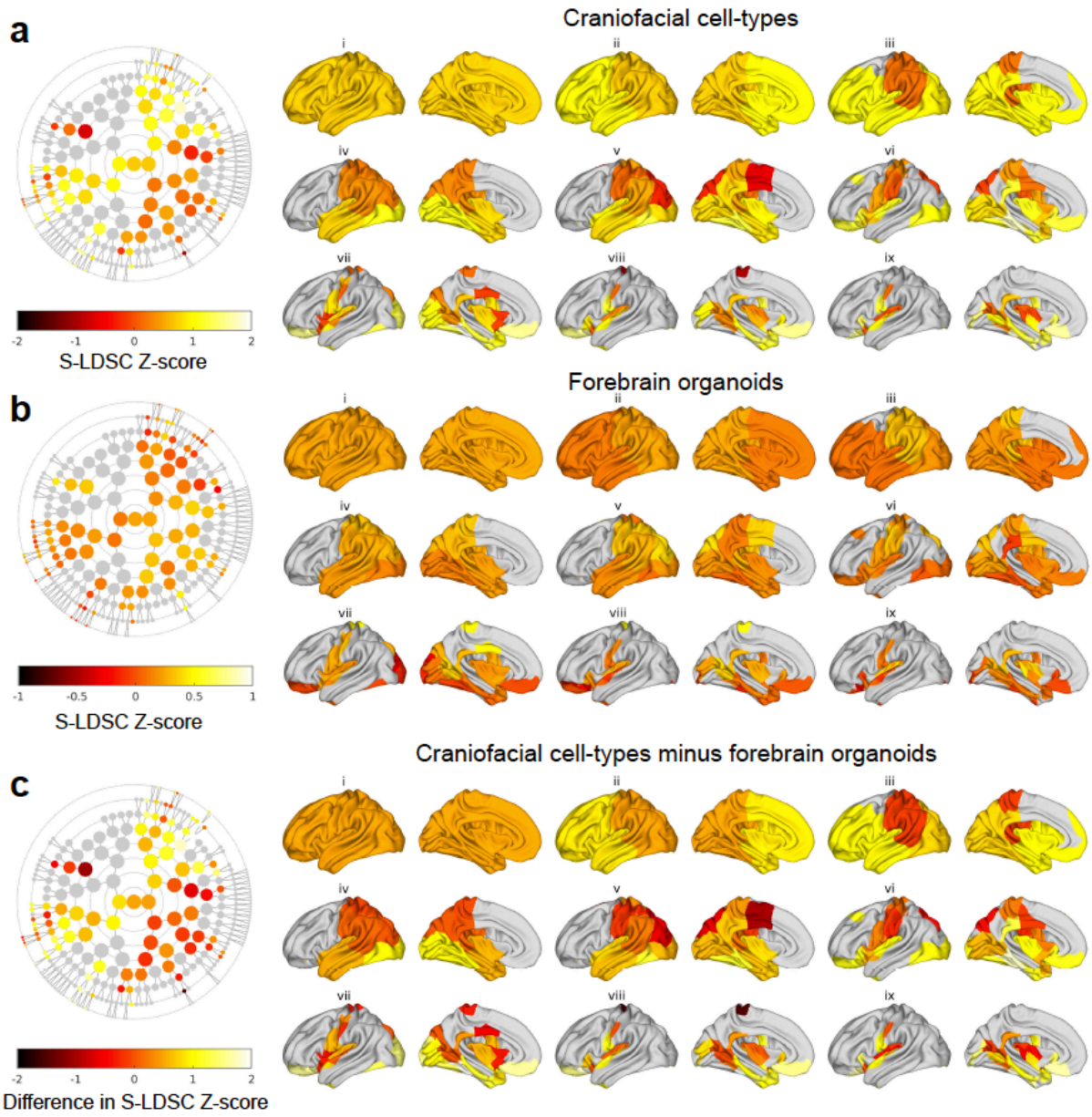
Supplementary Fig. 3 Overlap of global-to-local segmentation of brain shape with commonly used brain atlases. Left, heatmaps of percentages of each brain atlas region (y-axis) overlapping with global-to-local hierarchical brain segments in this study (x-axis). Right, heatmap of percentages of each by global-to-local hierarchical brain segments in this study (x-axis) overlapping with indicated brain atlas regions (y-axis).



Supplementary Fig. 4 Number of independent genome-wide significant associations discovered by hierarchical segments. Among segments of each hierarchical level (indicated by lower-case Roman numerals and corresponding to concentric circles in the polar dendrogram), the number of independent genome-wide significant associations is shown.



Supplementary Fig. 5 Regional associations of genome-wide significant loci for brain shape stratified by shared effects on facial shape. For the indicated sets of genome-wide significant brain shape loci, the number of associations with each brain segment (shown at hierarchical levels iv-vi) was plotted. The top and bottom 57 face-shared or brain-specific loci were chosen as 57 is the number of brain shape loci which have at least suggestive ($P < 5x10^{-7}$) association with face shape. Right-tailed, one-sided P-values were computed based on canonical correlation analysis (CCA) chi-squared statistics; exact p-values are available in Supplementary Table 2.



Supplementary Fig. 6 Partitioned heritability enrichments in craniofacial cell-types and brain organoids for brain shape within hierarchical segments. For each segment at the indicated hierarchical level, scaled S-LDSC Z-scores from all craniofacial (**a)** or brain organoid (**b)** annotations as indicated in Figure 4 were averaged, and the difference in mean Z-score between the two averages (**c**) was also computed.

Supplementary Note: Further details on Methods

UK Biobank data processing

Further details on the four-step procedure for processing raw MRI data are provided below: Second step: high dimensional cortical meshes were downsampled to lower resolution meshes of 32,492 3D vertices (average ~2mm spacing) and 64,980 triangular faces. Left and right hemispheres were aligned. All but one of the images were processed without error in this step. Third step: the vertices from the sub-cortical part of the surface were removed based on the sub-cortical vertex index provided by the Conte69 atlas. This yielded 29,759 vertices for each of the mid-cortical left and right surfaces. For each hemisphere and each individual, we also computed the centroid size as the average Euclidean distance of all mesh vertices to the point of gravity. In the remainder of this work, we refer to the mid-cortical surface as "brain shape." Fourth step: We first measured the Mahalanobis distance for each individual's mid-cortical surface to the overall average mid-cortical surface in a generalized Procrustes shape-space spanned by principal components that captures 98% of the total variation. From the Mahalanobis distance distribution, a z-score for each mid-cortical surface was established, and each mid-cortical surface with z-score ≥ 3 was manually inspected for meshing errors (e.g. triangles stretched too far or triangles folded). Filtering of UKB SNPs and individuals was performed as follows. First, European individuals were selected using principal component analysis (PCA) after excluding SNPs in linkage disequilibrium (LD) from the 1000G Phase 3 dataset (Plink 1.9, 50 variant window-size, 5 variant step size, 0.2 r^2). A k-nearest neighbor algorithm, using the first 25 reference ancestry principal components, was used to assign a 1000G super population label to each individual, and individuals with the 1000G super population EURO label were selected for analysis only. Second, we filtered imputed UKB SNPs by removing indels and multi-allelic SNPs, missing

genotypes across individuals (≤ 50%), minor allele frequency (<1%), and Hardy-Weinberg equilibrium ($p < 1e^{-6}$). Third, to remove related individuals and capture population structure we pruned the filtered SNP set for LD (Plink 1.9, 50 variant window-size, 5 variant step size, 0.2 r^2). Related individuals were removed when the proportion of identity by descent (IBD) was higher than 0.125.

For each of the covariate variables, except for assessment center, missing data was replaced by the average value of the respective variables. 26 subjects were removed due to extreme outlier covariates (>6 times the standard deviation) in weight (11 individuals), diastolic blood pressure (1 individual), systolic blood pressure (3 individuals), X-position of brain mask (6 individuals), Y-position of brain mask (4 individuals), Z-position of table/coil (1 individual).

ABCD study data preprocessing

Variants with missing rate greater than 10% as well as individuals with more than 10% of missing variants were excluded from phasing and imputation.

To assess ancestry, pre-phased QCed genotyped variants were filtered for Hardy-Weinberg Equilibrium ($P < 1 \times 10^{-6}$) and merged with the 1000 Genomes Phase 3 and the Human Genome Diversity Project reference panels. Variants in common between the datasets were pruned using a 1,500 kb window, 50 bp step size, and a 0.4 r^2 threshold. This pruned dataset, which contained 14,068 individuals both reference and ABCD datasets, was used subjected to PCA to construct an ancestry space. Using the eigenvalues that explained more than 5% of the total variance, an X-dimensional centroid was created from reference samples designated as having European ancestry. This created a “European centroid.” Only participants that were within 3 standard deviations of

the centroid were retained. These steps resulted in 5,622 individuals and 484,000 variants. Following phasing and imputation, only variants with INFO score > 0.7 wer retained, resulting in 15.3M imputed ABCD variants.

For the 5,622 individuals of primarily European ancestries, the genotyped and imputed variants were filtered by removing indels and multi-allelic SNPs, missing genotypes across individuals (<50%), minor allele frequency (<1%), and Hardy-Weinberg equilibrium ($p < 1e^{-6}$). In order to remove related individuals and capture population structure we pruned the filtered genotyped SNP set (Plink 1.9, 50 variant window-size, 5 variant step size, 0.2 r^2). Subsequently, 1,009 related individuals were removed when the proportion of identity by descent (IBD) was higher than 0.125. Finally, population structure was captured using PCA. Of the 4,613 unrelated subjects of European ancestries, 143 did not have a preprocessed brain image.

Global-to-local (G2L) segmentation of the mid-cortical surface

For each of the 285 brain segments, the set of surface vertices were subjected to a new GPA, such that a multivariate shape-space for each brain segment was constructed independently of the other segments. After GPA, each segment's shape-space was spanned by a multivariate orthogonal basis using PCA on the pooled x, y and z coordinates of the collection of superimposed vertices. Finally, we retained enough PCs to explain up to 80% of the total shape variation within each segment. This is in slight contrast to our previous work on facial shape, where we used parallel analysis (PA) instead. By choosing those PCs explaining up to 80% of the variation we typically retained 50% of the components otherwise retained using PA (e.g. 437 instead of ~1000 for the full hemisphere). However, the number of components retained using PA became computationally

intractable. Therefore, we opted to further reduce the number of PCs per brain segment, knowing that these certainly represent non-noisy shape variations, confirmed by PA.

Overlap of brain atlases with G2L segmentation

For each of the G2L levels separately, every brain surface vertex has a unique label of the G2L brain segment it belongs to at that level and a unique label of the atlas brain region it belongs to. Using these two labels, the normalized mutual information across all vertices provided a measure of overlap from 0 (no overlap) to 1 (complete overlap), for each G2L level with each of the three atlases. Additionally, each brain segment and each brain region defined a subset of vertices, and therefore, for each segment we defined the intersection of vertices with each brain region, and for each brain region we defined the intersection of vertices with each brain segment, expressed as percentages.

G2L multivariate genome-wide discovery

For each brain segment separately, canonical correlation analysis (CCA, canoncorr from Matlab 2019b), was used as a multivariate testing framework. CCA extracts the linear combination of PCs spanning the brain segment that correlates maximally with the SNP variant being tested, and therefore reveals a latent shape trait within the shape-space of the brain segment. The correlation of this latent shape trait with the SNP variant is tested for significance based on a χ^2 statistic (right-tail, one-sided test), with degrees of freedom equal to the dimensionality or number of principal components of the brain segment. Using CCA, we tested each SNP (n=9,705,931) individually under an additive genetic model in UKB (n=19,670) against each of the brain segments separately. Note that CCA does not adjust for covariates, but covariate adjustment was performed using PLSR

at the phenotyping stage. Additionally, we applied a similar correction for the covariates on each SNP, again using PLSR, excluding the covariates that were only relevant for the correction of imaging data (e.g. acquisition center).

The permutation procedure for determining the empirical number of GWAS was performed as follows. First, for a single SNP we randomly permuted the genotypes in UKB, essentially creating genotypes that have a noisy association with multivariate brain shape. Then, we performed the CCA associations of the randomized genotypes to each of the 285 brain segments and retained the lowest or "best" p-value out of the 285 p-values obtained. Step 1 and 2, were repeated 10,000 times. Subsequently, we divided 0.05 by the 5th percentile of the 10,000 permuted best CCA p-values, and this was done for each of the 472 SNPs. Based on these 472 outcomes, the mean number of empirical independent tests is 241.46 (11.09 standard deviation). We opted for this more conservative empirical estimation, and determined the study-wide significance threshold to be 2.0707×10^{-10} (i.e., $5 \times 10^{-8} / 241.46$).

Peak detection, overlap and annotations

Clumping of 38,630 genome-wide and 23,413 study-wide significant brain shape SNPs was performed as follows. First, starting with the best-associated or lead SNP (lowest p-value), SNPs within 10kb or within 1Mb but with $r^2 > 0.01$ were clumped into the same locus represented by the lead SNP. This process was repeated until all SNPs were assigned into 509 loci. Second, based on the lead SNPs only, a wider window of +/- 10Mb was tested for $r^2 > 0.01$, reducing the number of loci (n=502) by merging seven lead SNPs. Third, any locus with a singleton lead SNP below the study-wide threshold was removed (n=30). r^2 values were computed using UK Biobank genotypes.

ABCD replication testing

Replication was tested using a standard univariate linear regression (two-sided, regstats Matlab 2019b). This was done for each of the 466 lead SNPs for which the exact SNP or a proxy SNP (within 10kb or within 1Mb and $r^2 > 0.2$) was available for analysis in the ABCD cohort, and in each of the 285 segments that were associated at $P \leq 5 \times 10\text{-}8$, resulting in 3,586 replication tests. From all replication tests combined (n=3,586), we computed a 5% FDR-adjusted significance threshold[117] equal to $P \leq 0.0369$.

Clinical gene-panel overlap

We calculated the overlap between genes from clinical panels/subcategories/categories and different gene-sets allowing for a 200kb, 500kb or 1Mb window around the loci. Significance was tested by generating 10,000 random panels for each clinical panel subcategory/category with equal size using a list of 19,198 protein-coding genes. P-values were obtained by dividing "the number of times the overlap random panel and gene-set was larger than the overlap clinical gene-panel/subcategory/category and gene-set" and "number of random gene-panels created (10,000)". Clinical panels/subcategories/categories were interpreted as strongly or weakly enriched if they showed significance ($P < 0.05$) across three or two different gene-sets respectively.

Supplementary Note: LD Score Regression for Multivariate Traits

Jeffrey P. Spence

1 Main Theoretical Results

In this note, we show that LDscore regression [1] may be used on the results of GWAS on multivariate traits, albeit with a slight difference in interpretation. In the following we consider a D dimensional trait measured in a sample of N individuals and assume that there are P SNPs. We consider the standard additive model of phenotypes

$$\mathbf{Y} = \mathbf{XB} + \mathbf{E} \tag{1}$$

where $\mathbf{Y} \in \mathbb{R}^{N\times D}$ is the matrix of phenotypes; $\mathbf{X} \in \mathbb{R}^{N\times P}$ is the standardized genotype matrix; $\mathbf{B} \in \mathbb{R}^{P\times D}$ is the matrix of effect sizes, with $\mathbf{B}_{pd}$ representing the effect of SNP p on the d^{th} dimension of the trait; and $\mathbf{E} \in \mathbb{R}^{N\times D}$ is the residual matrix, representing environmental or measurement noise. For notational convenience, we will use $\mathbf{x}_j$ to represent the j^{th} column of the genotype matrix (i.e., the standardized genotypes of the N individuals at SNP j).

The goal of this analysis is to use the p-values reported by a multivariate GWAS to learn something about the heritability of the trait. Before beginning, however, we note that for a univariate trait, under a purely additive model, heritability is defined as the proportion of phenotypic variance, σ^2_P attributable to genetic variation σ^2_G. In the multivariate trait case, an appropriate definition is less clear because phenotypic variance is now represented by a $D \times D$ covariance matrix, Σ_P, and there is no single analogue of the proportion of variance explained by the genetic covariance matrix, Σ_G. The generalization that we will use is $\frac{1}{D}\text{trace}(\Sigma_G\Sigma_P^{-1})$, which reduces to the classical definition in the univariate case, and because $\Sigma_G \preceq \Sigma_P$, von Neumann's trace inequality shows that this number is bounded between 0 and 1, with the upper extreme being reached only when $\Sigma_G = \Sigma_P$. In some sense, this can be thought of as a coordinate system-free "average heritability" across the D dimensions of the trait. Indeed, if either Σ_G or Σ_P are diagonal (i.e., the coordinates are either genetically uncorrelated or phenotypically uncorrelated respectively) then $\frac{1}{D}\text{trace}(\Sigma_G\Sigma_P^{-1})$ is exactly the average of the univariate heritabilities of each dimension. Furthermore, this definition of heritability is invariant to scaling the dimensions of the trait, for example by changing units of measurement. In Section 2 we show that this generalization of heritability is, in fact, the only definition of heritability that satisfies all of these properties.

In order to make analytical progress, we introduce some assumptions. We assume N is large, and so we neglect terms of order $O(\frac{1}{N})$ that are induced by standardizing $\mathbf{Y}$ and $\mathbf{X}$. Like in the original derivation of LDscore regression [1] we assume that $\mathbf{X}$, $\mathbf{B}$, and $\mathbf{E}$ are all independent

random variables with the following moment conditions

$$\begin{aligned}
\mathbb{E}[\mathbf{X}] &= \mathbf{0}_{N\times P} \\
\mathbb{E}[\mathbf{B}] &= \mathbf{0}_{P\times D} \\
\mathbb{E}[\mathbf{E}] &= \mathbf{0}_{N\times D} \\
\mathbb{E}[\mathbf{X}_{ij}\mathbf{X}_{ik}] &= r_{jk} \\
\text{Var}[(\mathbf{B}_{j1},\ldots,\mathbf{B}_{jD})] &= \frac{1}{P}\begin{pmatrix} h_1^2 & \rho_{12} & \cdots & \rho_{1D} \\ \rho_{12} & h_2^2 & & \\ \vdots & & \ddots & \\ \rho_{1D} & & & h_D^2 \end{pmatrix} \\
\text{Var}[(\mathbf{E}_{i1},\ldots,\mathbf{E}_{iD})] &= \begin{pmatrix} 1-h_1^2 & \epsilon_{12} & \cdots & \epsilon_{1D} \\ \epsilon_{12} & 1-h_2^2 & & \\ \vdots & & \ddots & \\ \epsilon_{1D} & & & 1-h_D^2 \end{pmatrix}
\end{aligned}$$

and we assume that the effect sizes at different SNPs are uncorrelated, and that the errors across individuals are uncorrelated (but violations of this assumption are discussed below). We make the further assumption that $\mathbf{Y}^T\mathbf{Y} = N\mathbf{I}_D$. This assumption says that the multivariate trait is defined such that the dimensions are uncorrelated in the sample, and that each dimension is standardized to have mean zero and unit variance. In Section 1.2 we relax this assumption to allow for dependent columns. We also assume that hypothesis testing is performed using the following test statistic for SNP j, with estimated effect sizes at that SNP, $\widehat{\mathbf{b}}_j^T := \frac{1}{N}\mathbf{x}_j^T\mathbf{Y}$:

$$\chi_j^2 = N^2\widehat{\mathbf{b}}_j^T\left[(\mathbf{Y}-\mathbf{x}_j\widehat{\mathbf{b}}_j^T)^T(\mathbf{Y}-\mathbf{x}_j\widehat{\mathbf{b}}_j^T)\right]^{-1}\widehat{\mathbf{b}}_j, \tag{2}$$

which, under our assumption of $\mathbf{Y}^T\mathbf{Y} = N\mathbf{I}_D$, we show that this statistic reduces to

$$\chi_j^2 = \frac{N||\widehat{\mathbf{b}}_j||_2^2}{1-||\widehat{\mathbf{b}}_j||_2^2}$$

and in the univariate case is

$$\chi_j^2 = \frac{N\hat{\beta}_j^2}{1-\hat{\beta}_j^2}.$$

This assumption is mostly for convenience – in Section 1.3 we show that this is essentially equivalent to Wilks' Lambda, the default test statistic in many software packages [6]. For large N and $N \gg D$, the χ_j^2 statistic is approximately χ^2 distributed with D degrees of freedom. As a result, a p-value, p, from a GWAS may be transformed into the χ_j^2 statistic by taking the p^{th} upper quantile of the χ^2 distribution with D degrees of freedom.

We note that this statistic is defined differently from that in the original LDscore regression papers [1, 4] even in the case of a univariate trait, where they use

$$\chi_{\text{LDSC}}^2 = N\hat{\beta}_j^2.$$

The statistic in Equation 2 matches what is used in standard regression packages, whereas the statistic in the LDscore regression papers does not. When converting p-values to χ^2 statistics for LDscore regression, care should be taken that the result is the formula in Equation 2, *not* the statistic used in LDscore regression as defined in [1].

To avoid this confusion, we define the χ_j^2 statistic as would be produced by any standard regression package, and then frame our results in terms of this statistic.

Theorem 1. *Let the LD Score of SNP j be defined as*

$$\ell_j := \sum_{k=1}^{P} r_{jk}^2.$$

Then, with the assumptions described above, we have

$$\mathbb{E}\left[\frac{\chi_j^2}{D\left(1+\frac{\chi_j^2}{N}\right)}\right] = \frac{N-1}{P}\left(\frac{\sum_{d=1}^{D} h_d^2}{D}\right)\ell_j + 1 + O\left(\frac{1}{N}\right). \tag{3}$$

Proof. First, note that under the assumption that $\mathbf{Y}^T\mathbf{Y} = N\mathbf{I}$ we have

$$\begin{aligned}
\chi_j^2 &= N^2\widehat{\mathbf{b}}_j^T\left[(\mathbf{Y}-\mathbf{x}_j\widehat{\mathbf{b}}_j^T)^T(\mathbf{Y}-\mathbf{x}_j\widehat{\mathbf{b}}_j^T)\right]^{-1}\widehat{\mathbf{b}}_j \\
&= N^2\widehat{\mathbf{b}}_j^T\left[\mathbf{Y}^T\mathbf{Y}-\mathbf{Y}^T\mathbf{x}_j\widehat{\mathbf{b}}_j^T-\widehat{\mathbf{b}}_j\mathbf{x}_j^T\mathbf{Y}+\widehat{\mathbf{b}}_j\mathbf{x}_j^T\mathbf{x}_j\widehat{\mathbf{b}}_j^T\right]^{-1}\widehat{\mathbf{b}}_j \\
&= N^2\widehat{\mathbf{b}}_j^T\left[N\mathbf{I}_D - N\widehat{\mathbf{b}}_j\widehat{\mathbf{b}}_j^T\right]^{-1}\widehat{\mathbf{b}}_j \\
&= \frac{N||\widehat{\mathbf{b}}_j||_2^2}{1-||\widehat{\mathbf{b}}_j||_2^2}
\end{aligned}$$

where the third equality follows from the definition of $\widehat{\mathbf{b}}_j$, and the final equality follows from the Sherman-Morrison formula.

This then directly implies that

$$\frac{\chi_j^2}{D(1+\frac{\chi_j^2}{N})} = \frac{N}{D}||\widehat{\mathbf{b}}_j||_2^2.$$

We therefore seek to compute the expected value of $||\widehat{\mathbf{b}}_j||_2^2$, with

$$\begin{aligned}
\mathbb{E}\left[||\widehat{\mathbf{b}}_j||_2^2\right] &= \mathbb{E}\left[\widehat{\mathbf{b}}_j^T\widehat{\mathbf{b}}_j\right] \\
&= \frac{1}{N^2}\mathbb{E}\left[\mathbf{x}_j^T\mathbf{Y}\mathbf{Y}^T\mathbf{x}_j\right] \\
&= \frac{1}{N^2}\mathbb{E}\left[\mathbf{x}_j^T\left(\mathbf{X}\mathbf{B}+\mathbf{E}\right)\left(\mathbf{X}\mathbf{B}+\mathbf{E}\right)^T\mathbf{x}_j\right] \\
&= \frac{1}{N^2}\Big(\mathbb{E}\left[\mathbf{x}_j^T\mathbf{X}\mathbf{B}\mathbf{B}^T\mathbf{X}^T\mathbf{x}_j\right] + \mathbb{E}\left[\mathbf{x}_j^T\mathbf{X}\mathbf{B}\mathbf{E}^T\mathbf{x}_j\right] \\
&\qquad + \mathbb{E}\left[\mathbf{x}_j^T\mathbf{E}\mathbf{B}^T\mathbf{X}^T\mathbf{x}_j\right] + \mathbb{E}\left[\mathbf{x}_j^T\mathbf{E}\mathbf{E}^T\mathbf{x}_j\right]\Big).
\end{aligned}$$

But, by the independence of $\mathbf{B}$, $\mathbf{E}$ and $\mathbf{X}$ and the moment condition $\mathbb{E}[\mathbf{E}] = \mathbf{0}_{N\times D}$ we have

$$\mathbb{E}\left[\mathbf{x}_j^T\mathbf{X}\mathbf{B}\mathbf{E}^T\mathbf{x}_j\right] = \mathbb{E}\left[\mathbf{x}_j^T\mathbf{E}\mathbf{B}^T\mathbf{X}^T\mathbf{x}_j\right] = 0.$$

Hence,

$$\mathbb{E}\left[||\widehat{\mathbf{b}}_j||_2^2\right] = \frac{1}{N^2}\Big(\mathbb{E}\left[\mathbf{x}_j^T\mathbf{X}\mathbf{B}\mathbf{B}^T\mathbf{X}^T\mathbf{x}_j\right] + \mathbb{E}\left[\mathbf{x}_j^T\mathbf{E}\mathbf{E}^T\mathbf{x}_j\right]\Big).$$

Tackling the first term on the right hand side, we have

$$\begin{aligned}
\mathbb{E}\left[\mathbf{x}_j^T\mathbf{X}\mathbf{B}\mathbf{B}^T\mathbf{X}^T\mathbf{x}_j\right] &= \mathbb{E}\mathbb{E}\left[\mathbf{x}_j^T\mathbf{X}\mathbf{B}\mathbf{B}^T\mathbf{X}^T\mathbf{x}_j\middle|\mathbf{X}\right] \\
&= \mathbb{E}\left[\mathbf{x}_j^T\mathbf{X}\mathbb{E}\left[\mathbf{B}\mathbf{B}^T\middle|\mathbf{X}\right]\mathbf{X}^T\mathbf{x}_j\right] \\
&= \mathbb{E}\left[\mathbf{x}_j^T\mathbf{X}\mathbb{E}\left[\mathbf{B}\mathbf{B}^T\right]\mathbf{X}^T\mathbf{x}_j\right] \\
&= \frac{1}{P}\left(\sum_{d=1}^{D} h_d^2\right)\mathbb{E}\left[\mathbf{x}_j^T\mathbf{X}\mathbf{X}^T\mathbf{x}_j\right] \\
&= \frac{N^2}{P}\left(\sum_{d=1}^{D} h_d^2\right)\left(\ell_j + \frac{P-\ell_j}{N}\right) + O(1)
\end{aligned}$$

where we used that $\mathbb{E}[\mathbf{B}\mathbf{B}^T]_{jj'} = \sum_{d=1}^{D}\mathbb{E}\mathbf{B}_{jd}\mathbf{B}_{j'd} = \sum_{d=1}^{D}\frac{h_d^2}{P}$ if $j = j'$ and 0 otherwise by the fact that effect sizes at different loci are uncorrelated and that $\mathbb{E}[\mathbf{x}_j^T\mathbf{X}\mathbf{X}^T\mathbf{x}_j] = N^2(\ell_j + \frac{P-\ell_j}{N}) + O(1)$ which was shown in [1].

Meanwhile,

$$\begin{aligned}
\mathbb{E}\left[\mathbf{x}_j^T\mathbf{E}\mathbf{E}^T\mathbf{x}_j\right] &= \mathbb{E}\mathbb{E}\left[\mathbf{x}_j^T\mathbf{E}\mathbf{E}^T\mathbf{x}_j\middle|\mathbf{X}\right] \\
&= \mathbb{E}\left[\mathbf{x}_j^T\mathbb{E}\left[\mathbf{E}\mathbf{E}^T\middle|\mathbf{X}\right]\mathbf{x}_j\right] \\
&= \mathbb{E}\left[\mathbf{x}_j^T\mathbb{E}\left[\mathbf{E}\mathbf{E}^T\right]\mathbf{x}_j\right] \\
&= \left(\sum_{d=1}^{D} 1 - h_d^2\right)\mathbb{E}\left[\mathbf{x}_j^T\mathbf{x}_j\right] \\
&= N\left(\sum_{d=1}^{D} 1 - h_d^2\right)
\end{aligned}$$

where we used similar calculations to tackle $\mathbb{E}[\mathbf{E}\mathbf{E}^T]$ as we did to tackle $\mathbb{E}[\mathbf{B}\mathbf{B}^T]$, relying on the noise being uncorrelated across individuals.

Combining these results, we see

$$\mathbb{E}\left[||\widehat{\mathbf{b}}_j||_2^2\right] = \frac{1}{P}\left(\sum_{d=1}^{D} h_d^2\right)\left(1 - \frac{1}{N}\right)\ell_j + \frac{D}{N} + O\left(\frac{1}{N^2}\right),$$

which, after multiplying by N and dividing by D, implies

$$\mathbb{E}\left[\frac{\chi_j^2}{D\left(1 + \frac{\chi_j^2}{N}\right)}\right] = \frac{N-1}{P}\left(\frac{\sum_{d=1}^{D} h_d^2}{D}\right)\ell_j + 1 + O\left(\frac{1}{N}\right).$$

□

The practical implication of this theorem is that by regressing LD scores against the transformed χ_j^2 statistics from a multivariate GWAS, we are able to infer the average of the heritabilities of the dimensions of the trait.

It is clear from the proof that the assumption that errors are uncorrelated across individuals is not strictly necessary: like LDscore regression, violations of this assumption would result in changes to the intercept term, but not to the slope. As such, test statistic inflation due to effects such as population structure will get captured by the intercept term without biasing the slope.

1.1 Partitioning average heritability

While Theorem 1 assumes an infinitesimal model where each variant contributes equally to the average heritability, in reality there is reason to believe that SNPs with certain characteristics or SNPs in some regions of the genome may contribute more to heritability. For instance, SNPs that lie in open chromatin in relevant cell types might be expected to contribute more to heritability. In general, we may annotate each SNP as belonging to different categories, and we can then infer the average contribution to heritability of each distinct annotation, which may highlight which regions of the genome are important for the trait. These ideas were originally pioneered in the single dimension trait case in [4], and we extend those results to our present multidimensional trait case here.

To formalize this model, we partition the P SNPs into non-overlapping annotations, and we call this partitioning $\mathcal{C}$. Let $P(c)$ denote the number of SNPs in partition c, so that $\sum_{c\in\mathcal{C}} P(c) = P$. We maintain the same moment conditions as before, except now we have that for each annotation $c \in \mathcal{C}$, for each SNP $j \in c$,

$$\text{Var}\left[(\mathbf{B}_{j1},\ldots,\mathbf{B}_{jD})\right] = \frac{1}{P(c)}\begin{pmatrix} h_1^2(c) & \rho_{12}(c) & \cdots & \rho_{1D}(c) \\ \rho_{12}(c) & h_2^2(c) & & \\ \vdots & & \ddots & \\ \rho_{1D}(c) & & & h_D^2(c) \end{pmatrix},$$

and we define the the heritability of a dimension as the sum of the heritabilities contributed from each annotation:

$$h_d^2 := \sum_{c\in\mathcal{C}} h_d^2(c).$$

That is, we allow the distribution of effect sizes for SNPs in each annotation to have an arbitrary variance-covariance matrix determined by that annotation.

With this generalization of the assumptions of Theorem 1 we obtain the following generalization.

Theorem 2. *Under the assumptions listed above, and letting the annotation-specific LD score of SNP j and annotation $c \in \mathcal{C}$ be defined as*

$$\ell(j,c) := \sum_{k\in c} r_{jk}^2$$

we have

$$\mathbb{E}\left[\frac{\chi_j^2}{D\left(1+\frac{\chi_j^2}{N}\right)}\right] = (N-1)\left[\sum_{c\in\mathcal{C}}\frac{\ell(j,c)}{P(c)} \times \frac{\sum_{d=1}^D h_d^2(c)}{D}\right] + 1 + O\left(\frac{1}{N}\right). \tag{4}$$

Proof. From the proof of Theorem 1, we have that

$$\mathbb{E}\left[\frac{\chi_j^2}{D\left(1+\frac{\chi_j^2}{N}\right)}\right] = \frac{N}{D}||\widehat{\mathbf{b}}_j||_2^2$$

and

$$||\widehat{\mathbf{b}}_j||_2^2 = \frac{1}{N^2}\Big(\mathbb{E}\left[\mathbf{x}_j^T\mathbf{X}\mathbf{B}\mathbf{B}^T\mathbf{X}^T\mathbf{x}_j\right] + \mathbb{E}\left[\mathbf{x}_j^T\mathbf{E}\mathbf{E}^T\mathbf{x}_j\right]\Big).$$

The first term on the right hand side will need to be recalculated because of the different moment condition on $\mathbf{B}$, but the second term remains unchanged. To begin, note that $\mathbb{E}\left[\mathbf{B}\mathbf{B}^T\right]_{jj'} = 0$ if $j \neq j'$ by the independence of sites and the fact that $\mathbf{B}$ has mean zero. For the diagonal terms,

$$\begin{aligned}\mathbb{E}\left[\mathbf{B}\mathbf{B}^T\right]_{jj} &= \sum_{d=1}^D \mathbb{E}\mathbf{B}_{jd}^2 \\ &= \frac{1}{P(c(j))}\sum_{d=1}^D h_d^2(c(j)),\end{aligned}$$

where we wrote $c(j)$ for the partition that contains SNP j.

Then, using the independence of $\mathbf{B}$ and $\mathbf{X}$, and defining $\hat{r}_{jk} := \mathbf{x}_j^T\mathbf{x}_k/N$ we obtain

$$\begin{aligned}\mathbb{E}\left[\mathbf{x}_j^T\mathbf{X}\mathbf{B}\mathbf{B}^T\mathbf{X}^T\mathbf{x}_j\right] &= \mathbb{E}\left[\mathbf{x}_j^T\mathbf{X}\mathbb{E}\left[\mathbf{B}\mathbf{B}^T\right]\mathbf{X}^T\mathbf{x}_j\right] \\ &= N^2\sum_{c\in\mathcal{C}}\frac{\sum_{d=1}^D h_d^2(c)}{P(c)}\sum_{k\in c}\mathbb{E}\hat{r}_{jk}^2 \\ &= N^2\left[\sum_{c\in\mathcal{C}}\left(\ell(j,c) + \frac{P(c)-\ell(j,c)}{N}\right)\frac{\sum_{d=1}^D h_d^2(c)}{P(c)}\right] + O(1) \\ &= (N^2-N)\left(\sum_{c\in\mathcal{C}}\frac{\ell(j,c)}{P(c)}\sum_{d=1}^D h_d^2(c)\right) + N\left(\sum_{d=1}^D h_d^2\right) + O(1),\end{aligned}$$

where the third equality follows from the fact that $\mathbb{E}\hat{r}_{jk}^2 = r_{jk}^2 + (1-r_{jk}^2)/N + O(1/N^2)$, which was proved in [1].

Recall that

$$\mathbb{E}\left[\mathbf{x}_j^T\mathbf{E}\mathbf{E}^T\mathbf{x}_j\right] = N\left(\sum_{d=1}^D 1 - h_d^2\right) = ND - N\sum_{d=1}^D h_d^2$$

so combining we have

$$||\widehat{\mathbf{b}}_j||_2^2 = \left(1-\frac{1}{N}\right)\left(\sum_{c\in\mathcal{C}}\frac{\ell(j,c)}{P(c)}\sum_{d=1}^D h_d^2(c)\right) + \frac{D}{N} + O\left(\frac{1}{N^2}\right)$$

which implies that

$$\mathbb{E}\left[\frac{\chi_j^2}{D\left(1+\frac{\chi_j^2}{N}\right)}\right] = (N-1)\left[\sum_{c\in\mathcal{C}}\frac{\ell(j,c)}{P(c)} \times \frac{\sum_{d=1}^{D} h_d^2(c)}{D}\right] + 1 + O\left(\frac{1}{N}\right).$$

□

An interesting consequence of this definition of heritability enrichment is that it is invariant to the combinations of dimensions that each annotation affects – all that matters is the average heritability of each dimension. As a concrete example, consider the following two models. In the first model, the annotations are meaningless and variants in each annotation have the same distribution of effects on the trait. In the second model, the SNPs in each annotation affect only a single dimension of the trait, and each annotation affects a different dimension of the trait, but the heritability of each dimension is the same. Under both of these models, the average heritability across dimensions of the trait is the same for each annotation, and so there is no enrichment of heritability in any annotation in either model.

1.2 Traits with correlated dimensions

In the above, we assumed that $\mathbf{Y}$ was normalized and rotated such that $\mathbf{Y}^T\mathbf{Y} = N\mathbf{I}_D$. If $\mathbf{Y}$ is not normalized, we can perform the thin singular value decomposition of $\mathbf{Y} = \mathbf{U}\mathbf{S}\mathbf{V}^T$. Then, letting $\tilde{\mathbf{Y}} := \sqrt{N}\mathbf{U}$ we have $\tilde{\mathbf{Y}}^T\tilde{\mathbf{Y}} = N\mathbf{I}_D$ as required. We can then rewrite Equation 1 by noting that $\tilde{\mathbf{Y}} = \sqrt{N}\mathbf{Y}\mathbf{V}\mathbf{S}^{-1}$:

$$\tilde{\mathbf{Y}} = \mathbf{X}\tilde{\mathbf{B}} + \tilde{\mathbf{E}},$$

where $\tilde{\mathbf{B}} = \sqrt{N}\mathbf{B}\mathbf{V}\mathbf{S}^{-1}$ and $\tilde{\mathbf{E}} = \sqrt{N}\mathbf{E}\mathbf{V}\mathbf{S}^{-1}$. The proof of Theorem 1 requires us to compute $\mathbb{E}[\tilde{\mathbf{B}}\tilde{\mathbf{B}}^T]$ and $\mathbb{E}[\tilde{\mathbf{E}}\tilde{\mathbf{E}}^T]$. Below, we will write $\mathbf{\Sigma}_P = \frac{1}{N}\mathbf{Y}^T\mathbf{Y}$ for the phenotypic variation and $\mathbf{\Sigma}_G = P\text{Var}(\mathbf{B}_j)$ for the total genetic variance.

Beginning with $\mathbb{E}[\tilde{\mathbf{B}}\tilde{\mathbf{B}}^T]$ we have

$$\begin{aligned}\mathbb{E}[\tilde{\mathbf{B}}\tilde{\mathbf{B}}^T] &= N\mathbb{E}[\mathbf{B}\mathbf{V}\mathbf{S}^{-2}\mathbf{V}^T\mathbf{B}^T] \\ &= \text{trace}\left(\text{Var}(\mathbf{B}_j)\left(\frac{1}{N}\mathbf{Y}^T\mathbf{Y}\right)^{-1}\right)\mathbf{I}_P \\ &= \frac{1}{P}\text{trace}\left(\mathbf{\Sigma}_G\mathbf{\Sigma}_P^{-1}\right)\mathbf{I}_P.\end{aligned}$$

A similar calculation results in

$$\mathbb{E}[\tilde{\mathbf{E}}\tilde{\mathbf{E}}^T] = \text{trace}\left(\text{Var}(\mathbf{E}_i)\mathbf{\Sigma}_P^{-1}\right)\mathbf{I}_N.$$

Yet, under our additive model the phenotypic variation must equal the variance from the noise plus the genetic variance, and so we must have $\text{Var}(\mathbf{E}_i) = \Sigma_P - \Sigma_G$, ignoring terms of $O(1/N)$. Therefore,

$$\mathbb{E}[\tilde{\mathbf{E}}\tilde{\mathbf{E}}^T] = \mathbf{I}_N - \text{trace}\left(\mathbf{\Sigma}_G\mathbf{\Sigma}_P^{-1}\right)\mathbf{I}_N.$$

Using these results in the proofs of Theorems 1 results in the following generalization.

Corollary. *In the notation of Section 1.2, for general* $\frac{1}{N}\mathbf{Y}^T\mathbf{Y} = \mathbf{\Sigma}_P$*, we have*

$$\mathbb{E}\left[\frac{\chi_j^2}{1+\frac{\chi_j^2}{N}}\right] = \frac{N-1}{P}\text{trace}\left(\mathbf{\Sigma}_G\mathbf{\Sigma}_P^{-1}\right)\ell_j + D + O\left(\frac{1}{N}\right).$$

If we allow the distribution of effect sizes to change across genomic annotations like in Section 1.1, then we can consider the total contribution to genetic covariance of each annotation:

$$\mathbf{\Sigma}_G^c := P(c)\text{Var}\left(\mathbf{B}_j\right),$$

for any SNP $j \in c$, and we can let $\mathbf{\Sigma}_G := \sum_{c\in\mathcal{C}}\mathbf{\Sigma}_G^c$ denote the total contribution to genetic covariance across all SNPs. Following similar reasoning as above about $\mathbb{E}\left[\tilde{\mathbf{B}}\tilde{\mathbf{B}}^T\right]$ and $\mathbb{E}\left[\tilde{\mathbf{E}}\tilde{\mathbf{E}}^T\right]$ we see that we can simply replace $\sum_{d=1}^D h_d^2(c)$ by $\text{trace}\left(\mathbf{\Sigma}_G^c\mathbf{\Sigma}_P^{-1}\right)$ in the proof of Theorem 2 to obtain the following generalization.

Corollary. *In the notation of Section 1.2, for general* $\frac{1}{N}\mathbf{Y}^T\mathbf{Y} = \mathbf{\Sigma}_P$ *and allowing the distribution of effect sizes to change across a set of annotations,* $\mathcal{C}$*, that partitions the SNPs, we have*

$$\mathbb{E}\left[\frac{\chi_j^2}{1+\frac{\chi_j^2}{N}}\right] = (N-1)\left[\sum_{c\in\mathcal{C}}\text{trace}\left(\mathbf{\Sigma}_G^c\mathbf{\Sigma}_P^{-1}\right)\frac{\ell(j,c)}{P(c)}\right] + D + O\left(\frac{1}{N}\right).$$

1.3 Using p-values from tests based on other test statistics

In previous work on multivariate traits [3] an alternative test statistic to Equation 2 was used. In particular, testing was performed using Wilks' lambda which is the default option for canonical correlation analysis-based multivariate regression in many software packages [6]. Here, we show that the p-values generated by tests based on Wilks' lambda are approximately equivalent to those based on the test statistic in Equation 2. This section is largely a recap of classical results [5, 2].

Wilks' lambda arises in the general multivariate regression setting defined by Equation 1. In this setting we are interested in testing whether any of several null hypotheses is false. This is often referred to as an omnibus test. In particular, consider the following null hypothesis

$$H_0 : \mathbf{CBA} = \mathbf{D}$$

for matrices $\mathbf{C} \in \mathbb{R}^{Q\times P}$, $\mathbf{A} \in \mathbb{R}^{D\times D}$ and $\mathbf{D} \in \mathbb{R}^{Q\times D}$. We may then define the following matrices

$$\mathbf{S}_e := \mathbf{A}^T(\mathbf{Y} - \mathbf{X}\hat{\mathbf{B}})^T(\mathbf{Y} - \mathbf{X}\hat{\mathbf{B}})\mathbf{A}$$
$$\mathbf{S}_h := (\mathbf{C}\hat{\mathbf{B}}\mathbf{A} - \mathbf{D})^T(\mathbf{C}(\mathbf{X}^T\mathbf{X})^{-1}\mathbf{C}^T)^{-1}(\mathbf{C}\hat{\mathbf{B}}\mathbf{A} - \mathbf{D}).$$

Finally, letting $\lambda_1, \ldots, \lambda_K$ be the non-zero eigenvalues of $\mathbf{S}_e^{-1}\mathbf{S}_h$, Wilks' lambda is defined as

$$\Lambda_{\text{Wilks'}} := \prod_{k=1}^K \frac{1}{1+\lambda_k}.$$

To specialize to the present case, we note that for GWAS, the tests are actually run marginally, so the model is

$$\mathbf{Y} = \mathbf{x}_j \mathbf{b}_j^T + \mathbf{E},$$

and we test against the null hypothesis

$$H_0 : \mathbf{b}_j^T = \mathbf{0}_{1\times D}.$$

That means that in the above omnibus hypothesis setting we have that $\mathbf{C} = 1$, $\mathbf{A} = \mathbf{I}_D$, and $\mathbf{D} = \mathbf{0}_{1\times D}$. As a result,

$$\begin{aligned}\mathbf{S}_e &= (\mathbf{Y} - \mathbf{x}_j \widehat{\mathbf{b}}_j^T)^T (\mathbf{Y} - \mathbf{x}_j \widehat{\mathbf{b}}_j^T) \\ \mathbf{S}_h &= \widehat{\mathbf{b}}_j (\mathbf{x}_j^T \mathbf{x}_j)^{-1} \widehat{\mathbf{b}}_j^T = N \widehat{\mathbf{b}}_j \widehat{\mathbf{b}}_j^T.\end{aligned}$$

and so

$$\mathbf{S}_e^{-1}\mathbf{S}_h = N \left[(\mathbf{Y} - \mathbf{x}_j \widehat{\mathbf{b}}_j^T)^T (\mathbf{Y} - \mathbf{x}_j \widehat{\mathbf{b}}_j^T) \right]^{-1} \widehat{\mathbf{b}}_j \widehat{\mathbf{b}}_j^T.$$

This matrix is the product of a full rank matrix and a matrix with rank one, so it is rank one and has only one eigenvalue. Because the trace of a matrix is the sum of its eigenvalues, the sole eigenvalue of this matrix must be the trace. We may then use the cyclic property of trace to find

$$\begin{aligned}\text{trace}(\mathbf{S}_e^{-1}\mathbf{S}_h) &= N\text{trace}\left(\left[(\mathbf{Y} - \mathbf{x}_j \widehat{\mathbf{b}}_j^T)^T (\mathbf{Y} - \mathbf{x}_j \widehat{\mathbf{b}}_j^T) \right]^{-1} \widehat{\mathbf{b}}_j \widehat{\mathbf{b}}_j^T \right) \\ &= N\text{trace}\left(\widehat{\mathbf{b}}_j^T \left[(\mathbf{Y} - \mathbf{x}_j \widehat{\mathbf{b}}_j^T)^T (\mathbf{Y} - \mathbf{x}_j \widehat{\mathbf{b}}_j^T) \right]^{-1} \widehat{\mathbf{b}}_j \right) \\ &= N \widehat{\mathbf{b}}_j^T \left[(\mathbf{Y} - \mathbf{x}_j \widehat{\mathbf{b}}_j^T)^T (\mathbf{Y} - \mathbf{x}_j \widehat{\mathbf{b}}_j^T) \right]^{-1} \widehat{\mathbf{b}}_j.\end{aligned}$$

Therefore Wilks' lambda in this case is

$$\Lambda_{\text{Wilks'}} = \frac{1}{1 + N \widehat{\mathbf{b}}_j^T \left[(\mathbf{Y} - \mathbf{x}_j \widehat{\mathbf{b}}_j^T)^T (\mathbf{Y} - \mathbf{x}_j \widehat{\mathbf{b}}_j^T) \right]^{-1} \widehat{\mathbf{b}}_j},$$

and

$$\frac{1 - \Lambda_{\text{Wilks'}}}{\Lambda_{\text{Wilks'}}} = N \widehat{\mathbf{b}}_j^T \left[(\mathbf{Y} - \mathbf{x}_j \widehat{\mathbf{b}}_j^T)^T (\mathbf{Y} - \mathbf{x}_j \widehat{\mathbf{b}}_j^T) \right]^{-1} \widehat{\mathbf{b}}_j.$$

A classical result says that when $Q = 1$, as in our case,

$$\frac{1 - \Lambda_{\text{Wilks'}}}{\Lambda_{\text{Wilks'}}} \frac{N - D + 1}{D}$$

is F distributed with D and $N - D + 1$ degrees of freedom (e.g., Equation 8.19 in [2]). This implies that in the limit of large N,

$$(N - D + 1)\frac{1 - \Lambda_{\text{Wilks'}}}{\Lambda_{\text{Wilks'}}} \sim \chi^2 \text{ with } D \text{ degrees of freedom}$$

Therefore, compared to the statistic used in Theorem 1, χ_j^2, we have

$$(N - D + 1)\frac{1 - \Lambda_{\text{Wilks'}}}{\Lambda_{\text{Wilks'}}} = \left(1 - \frac{D}{N} + \frac{1}{N}\right) \chi_j^2 \approx \chi_j^2,$$

and p-values in both tests are computed under asymptotically equivalent distributions.

2 A multivariate generalization of heritability

Above we used $\frac{1}{D}\text{trace}\left(\boldsymbol{\Sigma}_G\boldsymbol{\Sigma}_P^{-1}\right)$ as a D-dimensional generalization of heritability for a genetic covariance matrix $\boldsymbol{\Sigma}_G$ and a phenotypic covariance matrix $\boldsymbol{\Sigma}_P$. There are many other sensible generalizations that also reduce to the univariate definition of heritability, for instance based on the Frobenius norm $||\cdot||_F$ or any operator norm $||\cdot||_{\text{op}}$. A few examples include:

- $\frac{||\boldsymbol{\Sigma}_G||_F}{||\boldsymbol{\Sigma}_P||_F}$
- $\frac{\text{trace}(\boldsymbol{\Sigma}_G)}{\text{trace}(\boldsymbol{\Sigma}_P)}$
- $\frac{||\boldsymbol{\Sigma}_G||_{\text{op}}}{||\boldsymbol{\Sigma}_P||_{\text{op}}}$
- $||\boldsymbol{\Sigma}_G\boldsymbol{\Sigma}_P^{-1}||_F$
- $||\boldsymbol{\Sigma}_G\boldsymbol{\Sigma}_P^{-1}||_{\text{op}}$
- $||\boldsymbol{\Sigma}_P^{-1/2}\boldsymbol{\Sigma}_G\boldsymbol{\Sigma}_P^{-1/2}||_F$
- $||\boldsymbol{\Sigma}_P^{-1/2}\boldsymbol{\Sigma}_G\boldsymbol{\Sigma}_P^{-1/2}||_{\text{op}}$

...

Indeed, because all univariate norms are proportional, for any matrix norm $||\cdot||_M$, any ratio of the form $\frac{||\boldsymbol{\Sigma}_G||_M}{||\boldsymbol{\Sigma}_P||_M}$, or any properly scaled matrix norm applied to $\boldsymbol{\Sigma}_G\boldsymbol{\Sigma}_P^{-1}$ or $\boldsymbol{\Sigma}_P^{-1/2}\boldsymbol{\Sigma}_G\boldsymbol{\Sigma}_P^{-1/2}$ will reduce to the univariate definition of heritability. Note that for positive semi-definite matrices, $\text{trace}(\cdot)$ is equal to the nuclear norm, and so $\text{trace}(\cdot)$ is also a norm on the relevant space. There are, of course, many other sensible ways to generalize heritability.

To provide some justification for our particular generalization, we list four simple properties that any generalization of heritability should possess and show that our generalization is the only measure that satisfies these four properties. We list these properties informally, as well as in formal mathematical statements about a heritability function, $h^2(\cdot,\cdot)$ that maps a genetic covariance matrix $\boldsymbol{\Sigma}_G$ and a phenotypic covariance matrix $\boldsymbol{\Sigma}_P$ to a scalar. Throughout when we say for all $\boldsymbol{\Sigma}_G$ and $\boldsymbol{\Sigma}_P$, we implicitly mean only such pairs that satisfy the constraints required under a non-degenrate additive genetic model: $0 \preceq \boldsymbol{\Sigma}_G \preceq \boldsymbol{\Sigma}_P$ and $0 \prec \boldsymbol{\Sigma}_P$. These constraints simply mean that the phenotypic variance is at least as great as the genetic variance for any combination of the dimensions of the trait, and the phenotypic variance of any combination of dimensions of the trait is strictly positive.

1. *Invariant to units of measurement*

   Any measure of heritability should be independent of the units with which the dimensions of the trait are measured. Mathematically, $h^2(\boldsymbol{\Sigma}_G, \boldsymbol{\Sigma}_P) = h^2(\mathbf{M}\boldsymbol{\Sigma}_G\mathbf{M}, \mathbf{M}\boldsymbol{\Sigma}_P\mathbf{M})$ for any diagonal matrix $\mathbf{M} \succ 0$, and for any $\boldsymbol{\Sigma}_P$, and $\boldsymbol{\Sigma}_G$.

2. *Coordinate-free*

   The way we choose to delineate the trait into different dimensions is arbitrary, especially with respect to genetic and phenotypic variance. Genetic variants or environmental effects

may act to alter specific combinations of dimensions as opposed to single dimensions. As such, the particular coordinate system we use to represent the trait should not impact our measure of heritability. Mathematically, $h^2(\mathbf{\Sigma}_G, \mathbf{\Sigma}_P) = h^2(\mathbf{U}\mathbf{\Sigma}_G\mathbf{U}^T, \mathbf{U}\mathbf{\Sigma}_P\mathbf{U}^T)$ for any orthogonal matrix $\mathbf{U}$.

3. *Linear in* $\mathbf{\Sigma}_G$

   If the variance attributable to genetics doubles, we would want the heritability to double. Similarly, the heritability of the trait attributable to two sets of independent variants should be the sum of the heritability attributed to each set.. That is, $h^2(c\mathbf{\Sigma}_G, \mathbf{\Sigma}_P) = ch^2(\mathbf{\Sigma}_G, \mathbf{\Sigma}_P)$ and $h^2(\mathbf{\Sigma}_G^{(1)} + \mathbf{\Sigma}_G^{(2)}, \mathbf{\Sigma}_P) = h^2(\mathbf{\Sigma}_G^{(1)}, \mathbf{\Sigma}_P) + h^2(\mathbf{\Sigma}_G^{(2)}, \mathbf{\Sigma}_P)$, for any scalar c, and any $\mathbf{\Sigma}_G$, $\mathbf{\Sigma}_G^{(1)}$, $\mathbf{\Sigma}_G^{(2)}$, and $\mathbf{\Sigma}_P$ such that the resulting matrices still obey the positive semidefinite ordering listed above.

4. *Maximized when* $\mathbf{\Sigma}_G = \mathbf{\Sigma}_P$

   When the genetic variance matches the phenotypic variance along all combinations of dimensions, the heritability should be 1. That is $h^2(\mathbf{\Sigma}, \mathbf{\Sigma}) = 1$ for any $\mathbf{\Sigma}$.

Theorem 3. *Let h^2 be a function that maps a pair of matrices, $\mathbf{\Sigma}_G$, and $\mathbf{\Sigma}_P$ such that $0 \preceq \mathbf{\Sigma}_G \preceq \mathbf{\Sigma}_P$ and $0 \prec \mathbf{\Sigma}_P$ to a scalar. Furthermore, assume that h^2 satisfies properties 1-4 listed above. Then,*

$$h^2(\mathbf{\Sigma}_G, \mathbf{\Sigma}_P) = \frac{1}{D}\text{trace}\left(\mathbf{\Sigma}_G\mathbf{\Sigma}_P^{-1}\right).$$

Proof. To begin, we can use the spectral decomposition $\mathbf{\Sigma}_P = \mathbf{U}_P\mathbf{\Lambda}_P\mathbf{U}_P^T$ and properties 1 and 2 to obtain:

$$\begin{aligned}
h^2(\mathbf{\Sigma}_G, \mathbf{\Sigma}_P) &= h^2(\mathbf{\Sigma}_G, \mathbf{U}_P\mathbf{\Lambda}_P\mathbf{U}_P^T) && (\textit{spectral decomposition})\\
&= h^2(\mathbf{U}_P^T\mathbf{\Sigma}_G\mathbf{U}_P, \mathbf{\Lambda}_P) && (\textit{Property 2})\\
&= h^2(\mathbf{\Lambda}_P^{-1/2}\mathbf{U}_P^T\mathbf{\Sigma}_G\mathbf{U}_P\mathbf{\Lambda}_P^{-1/2}, \mathbf{I}_D) && (\textit{Property 1})\\
&= h^2(\mathbf{\Sigma}_P^{-1/2}\mathbf{\Sigma}_G\mathbf{\Sigma}_P^{-1/2}, \mathbf{I}_D) && (\textit{spectral decomposition})
\end{aligned}$$

Therefore, $h^2(\mathbf{\Sigma}_G, \mathbf{\Sigma}_P)$ is equivalent to a function $\tilde{h}^2(\mathbf{\Sigma}_P^{-1/2}\mathbf{\Sigma}_G\mathbf{\Sigma}_P^{-1/2})$, that operates on a single matrix $0 \preceq \mathbf{\Sigma}_P^{-1/2}\mathbf{\Sigma}_G\mathbf{\Sigma}_P^{-1/2} \preceq \mathbf{I}_D$. It is clear that $\tilde{h}^2$ is linear in its argument by applying Property 3 to h^2:

$$\tilde{h}^2(\mathbf{M}_1 + \mathbf{M}_2) = h^2(\mathbf{M}_1 + \mathbf{M}_2, \mathbf{I}_D) = h^2(\mathbf{M}_1, \mathbf{I}_D) + h^2(\mathbf{M}_2, \mathbf{I}_D) = \tilde{h}^2(\mathbf{M}_1) + \tilde{h}^2(\mathbf{M}_2)$$

and

$$\tilde{h}^2(c\mathbf{M}) = h^2(c\mathbf{M}, \mathbf{I}_D) = ch^2(\mathbf{M}, \mathbf{I}_D) = c\tilde{h}^2(\mathbf{M}).$$

Furthermore, by Property 2 $\tilde{h}^2$ is also invariant to multiplication of its argument on the left and right by any orthogonal matrix, $\mathbf{U}$, and its inverse:

$$\tilde{h}^2(\mathbf{U}\mathbf{M}\mathbf{U}^T) = h^2(\mathbf{U}\mathbf{M}\mathbf{U}^T, \mathbf{U}\mathbf{I}_D\mathbf{U}^T) = h^2(\mathbf{M}, \mathbf{I}_D) = \tilde{h}^2(\mathbf{M})$$

Hence, we may diagonalize the argument of $\tilde{h}^2$ via its spectral decomposition, $\mathbf{M} = \mathbf{U}_M\mathbf{\Lambda}_M\mathbf{U}_M^T$:

$$\tilde{h}^2(\mathbf{M}) = \tilde{h}^2(\mathbf{U}_M\mathbf{\Lambda}_M\mathbf{U}_M^T) = \tilde{h}^2(\mathbf{\Lambda}_M),$$

but $\mathbf{\Lambda}_M$ only contains the eigenvalues of $\mathbf{M}$, so $\tilde{h}^2$ is a function of only the eigenvalues of its argument. Furthermore, permutation matrices are orthogonal, and so by left and right multiplying the argument by a permutation matrix and its inverse, we see that $\tilde{h}^2$ is unchanged. Therefore, $\tilde{h}^2$ is a linear, permutation-invariant function of the eigenvalues of its argument. The only functions that satisfies these properties are proportional to trace$(\cdot)$. This implies that $h^2(\mathbf{\Sigma}_G, \mathbf{\Sigma}_P) = C\text{trace}(\mathbf{\Sigma}_P^{-1/2}\mathbf{\Sigma}_G\mathbf{\Sigma}_P^{-1/2})$ for some constant of proportionality C. We may rearrange this to $h^2(\mathbf{\Sigma}_G, \mathbf{\Sigma}_P) = C\text{trace}(\mathbf{\Sigma}_G\mathbf{\Sigma}_P^{-1})$ by the cyclic property of the trace. Finally, Property 4 shows that the constant of proportionality must be $1/D$:

$$1 = h^2(\mathbf{\Sigma}, \mathbf{\Sigma}) = C\text{trace}(\mathbf{\Sigma}\mathbf{\Sigma}^{-1}) = C\text{trace}(\mathbf{I}_D) = CD \implies C = \frac{1}{D}.$$

Therefore, $h^2(\mathbf{\Sigma}_G, \mathbf{\Sigma}_P)$ can only be $\frac{1}{D}\text{trace}\left(\mathbf{\Sigma}_G\mathbf{\Sigma}_P^{-1}\right)$. □

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